IFW

Docket No. 247564US0/tca

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF: Yasuharu URANO, et al.

GAU: 1625

SERIAL NO: 10/754,541

EXAMINER:

FILED: January 12, 2004

FOR: HDAC INHIBITOR

REQUEST FOR PRIORITY

COMMISSIONER FOR PATENTS
ALEXANDRIA, VIRGINIA 22313

SIR:

☐ Full benefit of the filing date of U.S. Application Serial Number , filed , is claimed pursuant to the provisions of **35 U.S.C. §120**.

☐ Full benefit of the filing date(s) of U.S. Provisional Application(s) is claimed pursuant to the provisions of **35 U.S.C. §119(e)**: **Application No.** **Date Filed**

■ Applicants claim any right to priority from any earlier filed applications to which they may be entitled pursuant to the provisions of **35 U.S.C. §119**, as noted below.

In the matter of the above-identified application for patent, notice is hereby given that the applicants claim as priority:

COUNTRY	APPLICATION NUMBER	MONTH/DAY/YEAR
AUSTRALIA	2003900116	January 13, 2003
AUSTRALIA	2003905406	October 6, 2003

Certified copies of the corresponding Convention Application(s)

■ are submitted herewith

☐ will be submitted prior to payment of the Final Fee

☐ were filed in prior application Serial No. filed

☐ were submitted to the International Bureau in PCT Application Number
Receipt of the certified copies by the International Bureau in a timely manner under PCT Rule 17.1(a) has been acknowledged as evidenced by the attached PCT/IB/304.

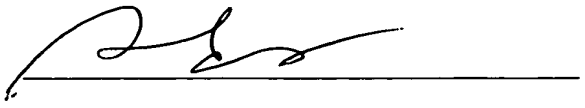
☐ (A) Application Serial No.(s) were filed in prior application Serial No. filed ; and

☐ (B) Application Serial No.(s)

- ☐ are submitted herewith
- ☐ will be submitted prior to payment of the Final Fee

Respectfully Submitted,

OBLON, SPIVAK, McCLELLAND,
MAIER & NEUSTADT, P.C.
Norman F. Oblon



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Patent Office
Canberra

I, LEANNE MYNOTT, MANAGER EXAMINATION SUPPORT AND SALES hereby certify that annexed is a true copy of the Provisional specification in connection with Application No. 2003900116 for a patent by FUJISAWA PHARMACEUTICAL CO., LTD. as filed on 13 January 2003.

WITNESS my hand this
Twenty-first day of January 2004

LEANNE MYNOTT
MANAGER EXAMINATION SUPPORT
AND SALES

CERTIFIED COPY OF
PRIORITY DOCUMENT

Regulation 3.2

Fujisawa Pharmaceutical Co., Ltd.

A U S T R A L I A

Patents Act 1990

PROVISIONAL SPECIFICATION

for the invention entitled:

"HDAC Inhibitor"

The invention is described in the following statement:

DESCRIPTION

HDAC INHIBITOR

TECHNICAL FIELD

The present invention relates to a compound which is useful as a medicament, and to a pharmaceutical composition comprising the same.

BACKGROUND ART

Histone deacetylases (hereinafter also referred as HDAC) are known to play an essential role in the transcriptional machinery for regulating gene expression, and they induce histone hyperacetylation and affect the gene expression. Therefore, they are useful as a therapeutic or prophylactic agent for diseases caused by abnormal gene expression, such as inflammatory disorders, diabetes, diabetic complications, homozygous thalassemia, fibrosis, cirrhosis, acute promyelocytic leukaemia (APL), organ transplant rejections, autoimmune diseases, protozoal infections, tumors and the like.

WO 01/38322 discloses an inhibitor of histone deacetylase represented by the following formula:

$$Cy\text{-}L^1\text{-}Ar\text{-}Y^1\text{-}C(O)\text{-}NH\text{-}Z$$

wherein

Cy is cycloalkyl, aryl, heteroaryl or heterocyclyl, each of which is optionally substituted;

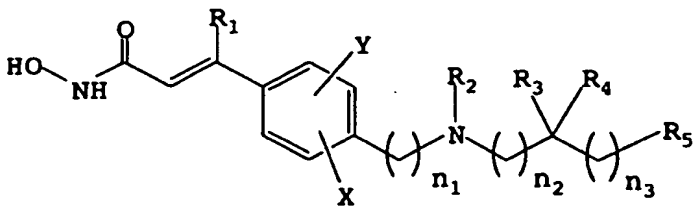
L^1 is $-(CH_2)_m-W-$, wherein m is an integer of 0 to 4, and W is selected from the group consisting of $-C(O)NH-$, $-S(O)_2NH-$ and the like;

Ar is optionally substituted arylene which is optionally fused to an aryl, heteroaryl ring and the like;

Y^1 is a chemical bond or a straight- or branched-chain saturated alkylene, wherein said alkylene is optionally substituted; and

Z is selected from the group consisting of anilinyl, pyridyl, thiadiazolyl and -O-M, wherein M is H or a pharmaceutically acceptable cation.

WO 0222577 discloses the following hydroxamate compound as a deacetylase inhibitor:



wherein

R_1 is H, halo, or a straight chain C_1-C_6 alkyl;

R_2 is selected from H, C_1-C_{10} alkyl, C_4-C_9 cycloalkyl, C_4-C_9 heterocycloalkyl, C_4-C_9 heterocycloalkylalkyl, cycloalkylalkyl, aryl, heteroaryl and the like;

R_3 and R_4 are the same or different and independently H, C_1-C_6 alkyl, acyl or acylamino, or R_3 and R_4 together with the carbon to which they are bound to represent C=O, C=S and the like, or R_2 together with the nitrogen to which it is bound and R_3 together with the carbon to which it is bound to form a C_4-C_9 heterocycloalkyl, a heteroaryl, a polyheteroaryl, a non-aromatic polyheterocycle, or a mixed aryl and non-aryl polyheterocycle ring;

R_5 is selected from H, C_1-C_6 alkyl and the like;

n, n_1, n_2 and n_3 are the same or different and independently selected from 0-6, when n_1 is 1-6, each carbon atom can be optionally and independently substituted with R_3 and/or R_4;

X and Y are the same or different and independently selected from H, halo, C_1-C_4 alkyl and the like;

or a pharmaceutically acceptable salt thereof.

SUMMARY OF THE INVENTION

The present invention relates to a novel compound which is useful as a medicament, and to a pharmaceutical composition comprising the same.

More particularly, the present invention relates to a compound which has a potent inhibitory effect on the activity of histone deacetylase.

The inventors of the present invention have also found that a histone deacetylase inhibitor, such as compound of formula (I) (hereinafter compound [I]), has a potent immunosuppressive effect and potent antitumor effect. Therefore, a histone deacetylase inhibitor, such as compound [I], is useful as an active ingredient of an immunosuppressant and an antitumor agent and useful as a

therapeutic or prophylactic agent for diseases such as inflammatory disorders, diabetes, diabetic complications, homozygous thalassemia, fibrosis, cirrhosis, acute promyelocytic leukaemia (APL), organ transplant rejections, autoimmune diseases, protozoal infections, tumors and the like.

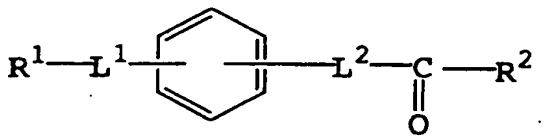
Accordingly, one object of the present invention is to provide a compound which has biological activities for treating or preventing the diseases as stated above.

A further object of the present invention is to provide a pharmaceutical composition containing the compound [I] as an active ingredient.

A yet further object of the present invention is to provide use of the histone deacetylase inhibitors, such as compound [I], for treating and preventing the diseases as stated above.

A yet further object of the present invention is to provide a commercial package comprising the pharmaceutical composition containing the compound [I] and a written matter associated therewith, the written matter stating that the pharmaceutical composition may or should be used for treating or preventing the diseases as stated above.

Thus, the present invention provides a compound of the formula (I):



(I)

wherein

R^1 is N-containing condensed heterocyclic ring optionally substituted with one or more suitable substituent(s),

R^2 is hydroxyamino,

L^1 is $-(CH_2)_n-$ (wherein n is an integer of 0 to 6) optionally substituted with one or more suitable substituent(s), and

L^2 is lower alkenylene,

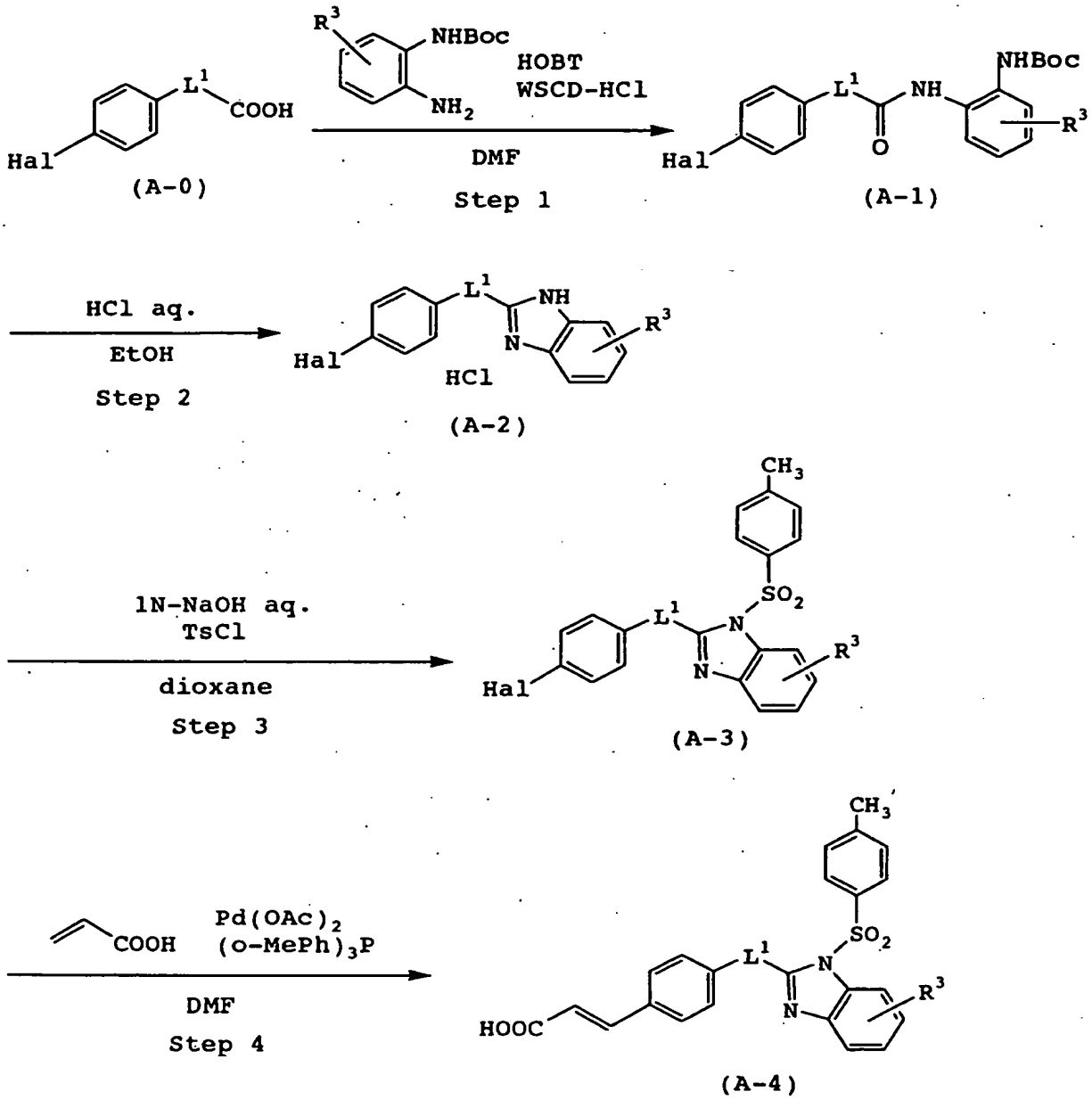
or a salt thereof.

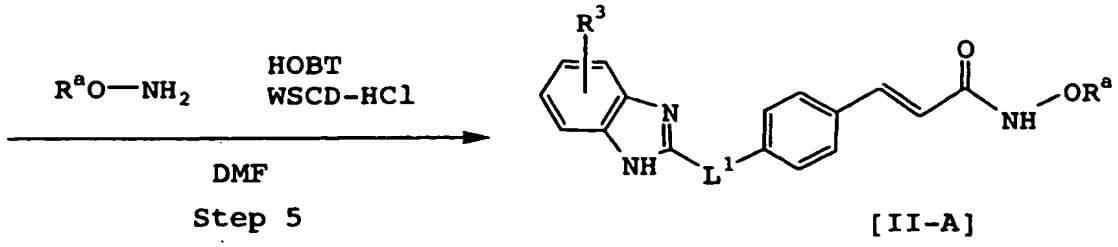
The compound [I] and a salt thereof can be prepared by the process as illustrated in the following reaction schemes.

In the following Processes, the Compound [I-1] is also included in the scope of the Compound [I], and the Compound [II-A],

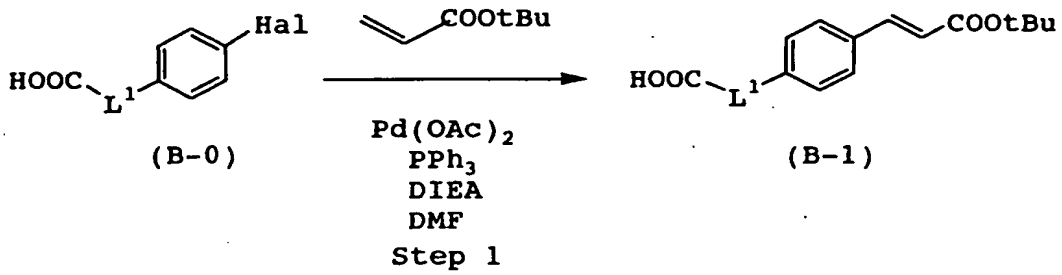
[II-B], [II-C], [II-C'] and [II-D] are also included in the scope of the Compound [II].

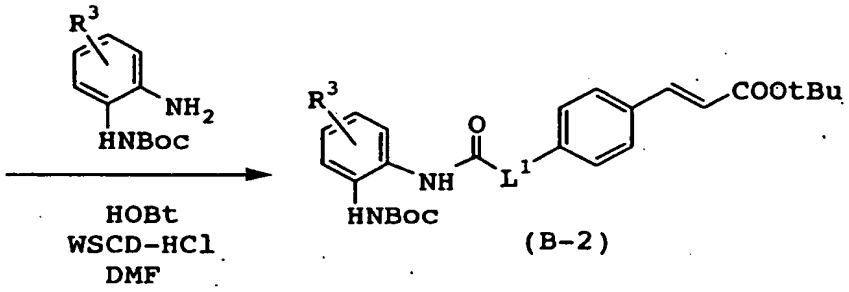
Process A

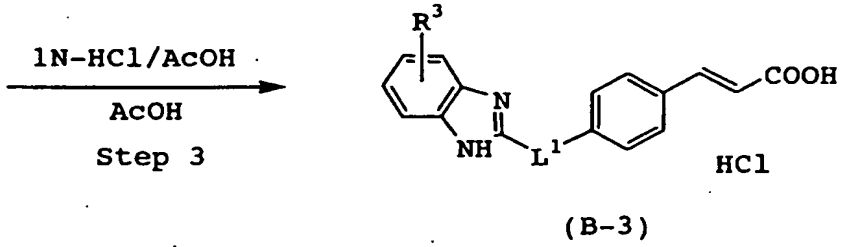


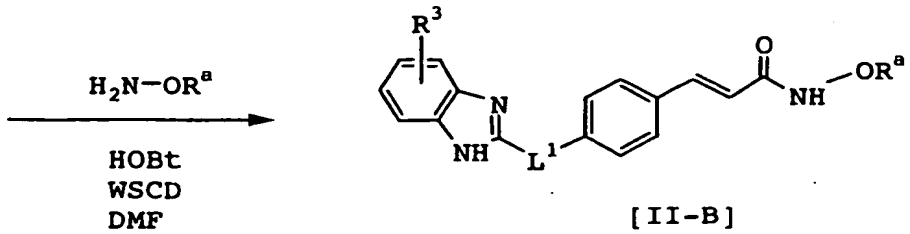

R^aO—NH2
HOBT
WSCD-HCl
DMF
Step 5
[II-A]

Process B

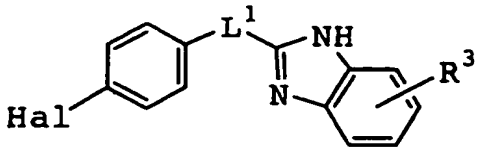

Hal
COOtBu
HOOC
L1
(B-0)
Pd(OAc)2
PPh3
DIEA
DMF
Step 1
(B-1)


R3
NH2
HNBoc
HOBt
WSCD-HCl
DMF
Step 2
COOtBu
NH
L1
(B-2)

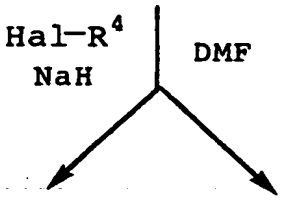

1N-HCl/AcOH
AcOH
Step 3
COOH
HCl
(B-3)

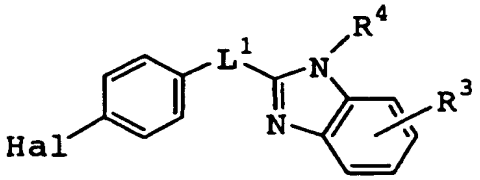

H2N—OR^a
HOBt
WSCD
DMF
Step 4
[II-B]

Process C

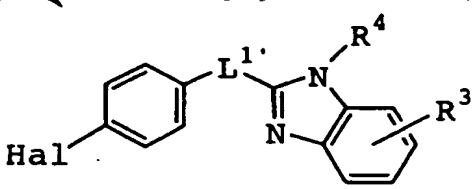


(A-2')



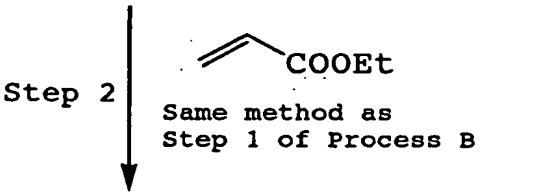


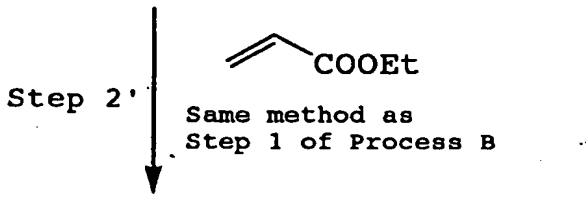
and

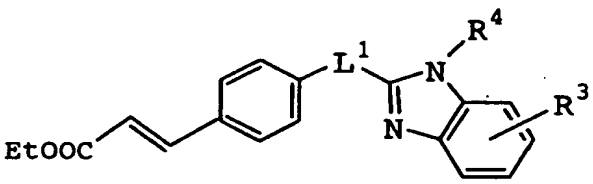


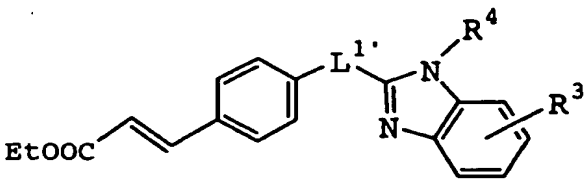
(C-1)

(C-1')



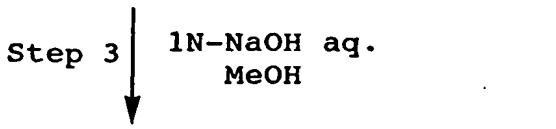


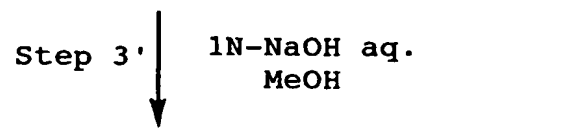


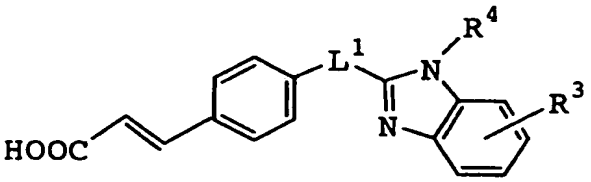


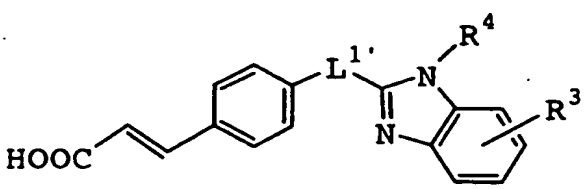
(C-2)

(C-2')



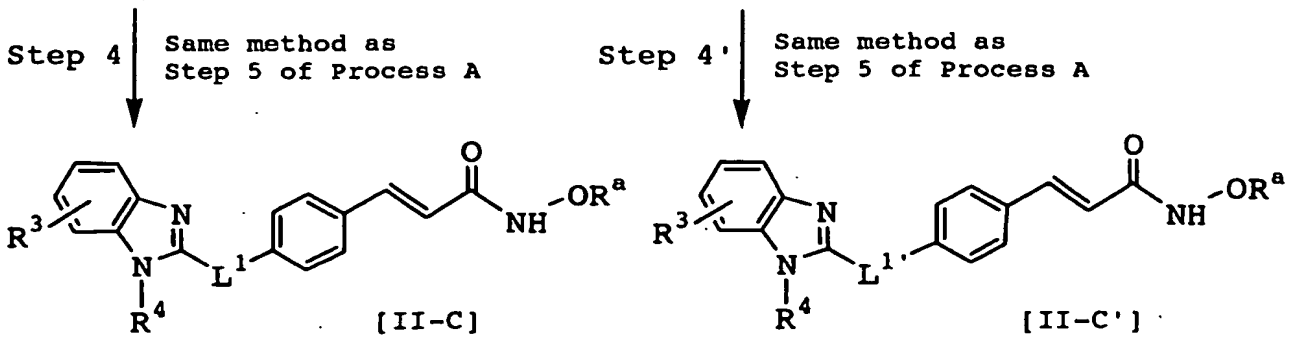




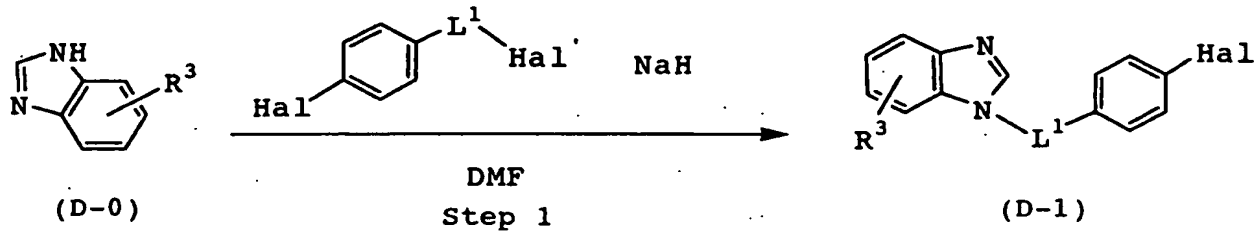


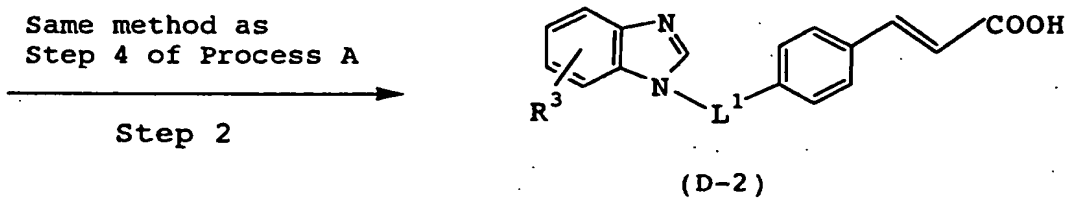
(C-3)

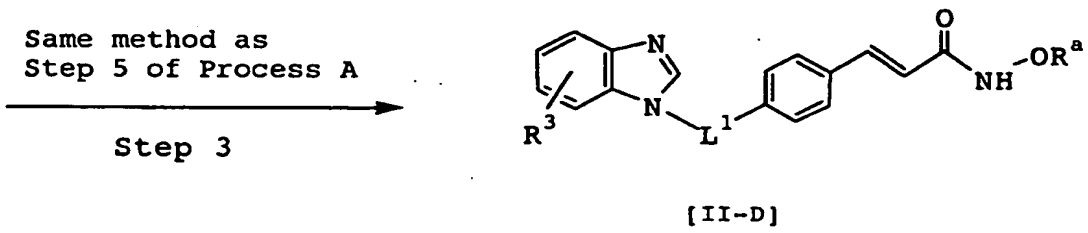
(C-3')


Step 4
Same method as
Step 5 of Process A
Step 4'
Same method as
Step 5 of Process A
[II-C]
[II-C']

Process D


NaH
DMF
Step 1
(D-0)
(D-1)


Same method as
Step 4 of Process A
Step 2
(D-2)

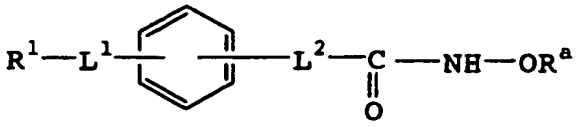

Same method as
Step 5 of Process A
Step 3
[II-D]

wherein R^1, R^2, L^1 and L^2 are as defined above,
R^3 is hydrogen or a substituent selected from the group consisting of lower alkyl and aryl,
R^4 is hydrogen or a substituent selected from the group consisting of alkyl and aryl(lower)alkyl,
$L^{1'}$ is L^1 in which one of the carbon atoms is substituted with R^4 (wherein R^4 is as defined above), and
R^a is a hydroxy protective group.

In the above-mentioned Processes A, B, C and D, each of the starting compounds can be prepared, for example, according to the procedures as illustrated in Preparations in the present specification or in a manner similar thereto. For example, the Compounds (A-1), (A-2), (A-3) and (A-4) can be obtained by the procedures as illustrated in Preparations 1, 2, 3 and 4 respectively, the Compounds (B-1), (B-2) and (B-3) can be obtained by the procedures as illustrated in Preparations 6, 7 and 8 respectively, the Compound (C-1) and (C-1') can be obtained by the procedure as illustrated in Preparation 10, the Compound (C-2) and (C-3) can be obtained by the procedure as illustrated in Preparations 11 and 12 respectively, the Compound (C-2') and (C-3') can be obtained by the procedure as illustrated in Preparations 23 and 24 respectively, and the Compound (D-1) and (D-2) can be obtained by the procedure as illustrated in Preparations 20 and 21 respectively. The Compounds [II-A], [II-B], [II-C], [II-C'] and [II-D] can be obtained, for example, by the procedure as illustrated in Preparations 5, 9, 13, 25 and 22 respectively.

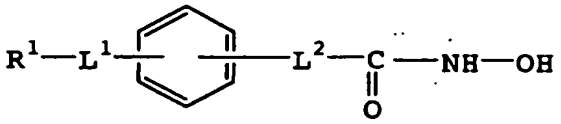
The Compound [I] of the present invention is obtained from Compound [II], for example, according to the following process.

Process 1



[II]

deprotection of hydroxy



[I]

wherein R^1, R^2, L^1, L^2 and R^a are as defined above.

The Compound [I] is obtained by deprotecting the hydroxy group of the Compound [II].

The reaction may be carried out in the presence of acid, for example, hydrogen chloride solution (e.g. hydrogen chloride in solvent such as methanol, dioxane, ethyl acetate, diethyl ether, etc.), acetic acid, p-toluenesulfonic acid, boric acid and the like.

Optionally, one or more suitable solvent(s) for the deprotection is(are) used. Such solvent include, for example, methanol, ethanol, ethyl acetate, dioxane, diethyl ether, acetic acid and the like.

The temperature of the reaction is not critical and the reaction is usually carried out from under cooling to heating.

This Process is exemplified by Example 1 and the like.

When the compound [I] has stereoisomers, such isomers are also encompassed in the present invention.

The compound [I] may form a salt, which is also encompassed in the present invention. For example, when a basic group such as an amino group is present in a molecule, the salt is exemplified by an acid addition salt (e.g. salt with an inorganic acid such as hydrochloric acid, hydrobromic acid, sulfuric acid, and the like, salt with an organic acid such as methanesulfonic acid, fumaric acid, maleic acid, mandelic acid, citric acid, salicylic acid, and

the like) is exemplified, and when an acidic group such as carboxyl group is present, a basic salt (e.g. salt with a metal such as sodium, potassium, calcium, magnesium, aluminium, and the like, a salt with amino acid such as lysine, and the like), and the like.

In addition, solvates of the compound [I] such as hydrate, ethanolate, and the like, are also encompassed in the present invention.

Suitable examples and illustration of the various definitions in the above and subsequent descriptions, which the present invention intends to be included within the scope thereof, are explained in detail as follows:

The term "halogen", "halo" and "Hal" include fluorine, chlorine, bromine, and iodine.

The term "lower" used in the description is intended to mean 1 to 6 carbon atoms, unless otherwise indicated.

Suitable example of "one or more" is the number of 1 to 6, preferably 1 to 3.

Suitable examples of "lower alkyl" include straight or branched one having 1 to 6 carbon atom(s), such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, tert-pentyl, neopentyl, hexyl, isohexyl and the like.

Suitable examples of "lower alkoxy" include straight or branched one having 1 to 6 carbon atom(s), such as methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec-butoxy, tert-butoxy, pentyloxy, tert-pentyloxy, neopentyloxy, hexyloxy, isohexyloxy and the like.

Suitable examples of "halo(lower)alkyl" include lower alkyl substituted with 1 to 3 halogen atom(s), for example, monochloromethyl, dichloromethyl, trichloromethyl, monofluoromethyl, difluoromethyl, trifluoromethyl, monobromomethyl, dibromomethyl, tribromomethyl, monochloroethyl, dichloroethyl, trichloroethyl, monofluoroethyl, difluoroethyl, trifluoroethyl and the like.

Suitable examples of "lower alkenylene" may include straight or branched one having 1 to 6 carbon atom(s), such as vinylene, 1-methylvinylene, 2-methylvinylene, 1-propenylene, 2-propenylene, 2-methyl-1-propenylene, 2-methyl-2-propenylene, 1-butenylene, 2-butenylene, 3-butenylene, 1-pentenylene, 2-pentenylene, 3-pentenylene, 4-pentenylene, 1-hexenylene, 2-hexenylene, 3-

hexenylene, 4-hexenylene, 5-hexenylene and the like. Suitable lower alkenylene for L^2 is, for example, vinylene, 1-methylvinylene, 2-methylvinylene and the like.

Suitable examples of "aryl" include C_6-C_{16} aryl such as phenyl, naphthyl, anthryl, pyrenyl, phenanthryl, azulenyl and the like.

Suitable examples of "aryloxy" include C_6-C_{16} aryloxy such as phenoxy, naphthyloxy, anthryloxy, pyrenyloxy, phenanthryloxy, azulenyloxy and the like.

Suitable examples of aryl(lower)alkyl include phenyl(C_1-C_6)alkyl such as benzyl, phenethyl, phenylpropyl, phenylbutyl, phenylhexyl and the like, naphthyl(C_1-C_6)alkyl such as naphthylmethyl, naphthylethyl, naphthylpropyl, naphthylbutyl, naphthylpentyl, naphtylhexyl and the like.

As used herein, "heteroaryl" include groups having 5 to 14 ring atoms and π electrons shared in a cyclic array and having, in addition to carbon atoms, 1 to 3 heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur. Suitable "heteroaryl" include, for example, thienyl, benzothienyl, furyl, benzofuryl, dibenzofuryl, pyrrolyl, imidazolyl, pyrazolyl, pyridyl, pyrazinyl, pyrimidinyl, indolyl, quinolyl, isoquinolyl, quinoxalinyl, tetrazolyl, oxazolyl, thiazolyl, isoxazolyl and the like, in which the preferred one is pyridyl.

The "heteroaryl" and "(lower)alkyl" of the "heteroaryl(lower)alkyl" are similar to that exemplified for the "heteroaryl" and "(lower)alkyl" respectively, and the preferred examples of the "heteroaryl(lower)alkyl" include, for example, pyridylmethyl, pyridylethyl, quinolylmethyl and the like.

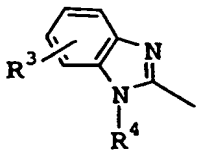
Each of the two "(lower)alkyl" of the "(lower)alkyl-carbonyl(lower)alkyl" is similar to that exemplified for the "(lower)alkyl", and the preferred examples of the "(lower)alkyl-carbonyl(lower)alkyl" include, for example, acetylmethyl, ethylcarbonylmethyl and the like.

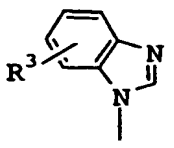
Suitable "N-containing condensed heterocyclic ring" for the "N-containing condensed heterocyclic ring optionally substituted with one or more substituent(s)" include, for example, indolyl, isoindolyl, indolidinyl, benzimidazolyl, quinolyl, isoquinolyl, indazolyl, benzotriazolyl, quinoxalinyl, imidazopyridyl (e.g.,

imidazo[4,5-c]pyridyl and the like), tetrahydroimidazopyridyl (e.g., 4,5,6,7-tetrahydro[4,5-c]pyridyl and the like), 7-azabicyclo[2.2.1]heptyl, 3-azabicyclo[3.2.2]nonanyl, pyridoimidazolyl (e.g. pyrido[3,2-d]imidazolyl, pyrido[4,3-d]imidazolyl and the like), azabenzimidazolyl and the like. and the like. The N-containing condensed heterocyclic ring suitable for R^1 of the present invention is, for example, benzimidazolyl and the like.

Suitable substituents for the "N-containing condensed heterocyclic ring optionally substituted with one or more substituent(s)" include, for example, lower alkyl (e.g. methyl, ethyl, propyl, butyl and the like), lower alkoxy (e.g. methoxy, ethoxy, propoxy, butoxy and the like), aryl (e.g. phenyl, naphthyl and the like), heteroaryl (e.g. pyridyl, pyrazinyl, pyrimidinyl, indolyl, quinolyl, isoquinolyl and the like), aryl(lower)alkyl (e.g. benzyl, phenetyl and the like), amino, carboxy, halo(lower)alkyl (e.g. trihalo(lower)alkyl such as trifluoromethyl and the like), aryloxy (e.g. phenoxy, naphthyloxy and the like), halogen (e.g. fluoro, chloro, bromo, iodo and the like), cyano, heteroaryl(lower)alkyl (e.g. pyridyl(lower)alkyl such as pyridylmethyl and the like), lower alkyl-carbonyl(lower)alkyl (e.g. acetylmethyl and the like) and the like, in which the preferred are methyl, chloro, phenyl, benzyl and the like. The "N-containing condensed heterocyclic ring" may be substituted with one or more of the above-mentioned substituent(s) on the carbon atom(s) and/or nitrogen atom(s) thereof.

Specifically, the preferred N-containing condensed heterocyclic ring optionally substituted with one or more substituent(s) is, for example, represented by the following formula



or


In the above formula, R^3 is hydrogen or a group selected from the group consisting of lower alkyl (e.g. methyl, ethyl, propyl, butyl and the like), lower alkoxy (e.g. methoxy, ethoxy, propoxy, butoxy and the like), aryl (e.g. phenyl, naphthyl and the like),

halogen, amino, aryl(lower)alkyl (e.g. benzyl, phenetyl and the like), heteroaryl (e.g. pyridyl, pyrazinyl, pyrimidinyl, indolyl, quinolyl, isoquinolyl and the like), cyano and carboxy. Preferably, R^3 is hydrogen or a group selected from the group consisting of lower alkyl and aryl.

In the above formula, R^4 is hydrogen or a group selected from the group consisting of lower alkyl (e.g. methyl, ethyl, propyl, butyl and the like), aryl(lower)alkyl(e.g. benzyl, phenetyl and the like), heteroaryl(lower)alkyl (e.g. pyridyl(lower)alkyl such as pyridylmethyl and the like) and lower alkyl-carbonyl(lower)alkyl (e.g. acetylmethyl and the like). Preferably, R^4 is hydrogen or a group selected from the group consisting of lower alkyl and aryl(lower)alkyl.

Suitable "n" of the "$-(CH_2)_n-$" for L^1 is an integer of 0 to 6, preferably 1 or 2. The "$-(CH_2)_n-$" optionally substituted with one or more suitable substituent(s) such as lower alkyl (e.g. methyl, ethyl, propyl, butyl and the like), lower alkoxy (e.g. methoxy, ethoxy, propoxy, butoxy and the like), aryl(lower)alkyl (e.g. benzyl and the like) and the like.

Suitable "hydroxy protecting group" is as follows:
lower alkyl such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, pentyl, hexyl, and the like, preferably methyl;
lower alkoxy(lower)alkyl (e.g. methoxymethyl and the like);
lower alkoxy(lower)alkoxy(lower)alkyl (e.g. 2-methoxyethoxymethyl and the like);
ar(lower)alkyl in which the aryl portion is optionally substituted with one or more suitable substituent(s) (e.g. benzyl (Bn), p-methoxybenzyl, m, p-dimethoxybenzyl, and the like), preferably benzyl;
ar(lower)alkoxy(lower)alkyl in which the aryl portion is optionally substituted with one or more suitable substituent(s) (e.g. benzyloxymethyl, p-methoxybenzyloxymethyl, and the like);
(lower)alkylthio(lower)alkyl (e.g. methylthiomethyl, ethylthiomethyl, propylthiomethyl, isopropylthiomethyl, butylthiomethyl, isobutylthiomethyl, hexylthiomethyl, and the like), and the like, preferably methylthiomethyl;
trisubstituted silyl such as tri(lower)alkylsilyl (e.g. trimethylsilyl, triethylsilyl, tributylsilyl, tert-

butyldimethylsilyl, tri-tert-butylsilyl, and the like), lower alkyldiarylsilyl (e.g. methyldiphenylsilyl, ethyldiphenylsilyl, propyldiphenylsilyl, tert-butyldiphenylsilyl (TBDPS), and the like), and the like, preferably tert-butyldimethylsilyl (TBDMS) and tert-butyldiphenylsilyl;
heterocyclic group (e.g. tetrahydropyranyl and the like);
acyl as described below [e.g. aliphatic acyl such as lower alkanoyl (e.g. acetyl, propanoyl, pivaloyl, and the like); aromatic acyl (e.g. benzoyl (Bz), toluoyl, naphthoyl, fluorenylcarbonyl and the like); lower alkoxycarbonyl (e.g. methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, isobutoxycarbonyl, t-butoxycarbonyl, pentyloxycarbonyl, hexyloxycarbonyl, and the like), and the like;
ar(lower)alkoxycarbonyl in which the aryl portion is optionally substituted with one or more suitable substituent(s) (e.g. benzyloxycarbonyl, bromobenzyloxycarbonyl and the like);
lower alkylsulfonyl (e.g. methylsulfonyl, ethylsulfonyl, and the like);
lower alkoxysulfonyl (e.g. methoxysulfonyl, ethoxysulfonyl, and the like);
ar(lower)alkanoyl (e.g. phenylacetyl, phenylpropanoyl, phenylbutanoyl, phenylisobutanoyl, phenylpentanoyl, phenylhexanoyl, naphthylacetyl, naphthylpropanoyl, naphthylbutanoyl, naphthylisobutanoyl, naphthylpentanoyl, naphthylhexanoyl, and the like);
ar(lower)alkenoyl such as ar(C_3-C_6)alkenoyl (e.g. phenylpropenoyl, phenylbutenoyl, phenylmethacryloyl, phenylpentenoyl, phenylhexenoyl, naphthylpropenoyl, naphthylbutenoyl, naphthylmethacryloyl, naphthylpentenoyl, naphthylhexenoyl, and the like); and the like];
lower alkenyl (e.g. vinyl, allyl, and the like); and the like. The preferable hydroxy protective group for the present invention is, for example, tetrahydropyranyl, trimethylsilyl, t-butyldimethylsilyl.

The following abbreviations are also used in the present specification: Boc (t-butyloxycarbonyl); HOBT (1-hydroxybenzotriazole); WSCD (1-ethyl-3-(3'-dimethylaminopropyl)-carbodiimide); DMF (N,N-dimethylformamide); aq. (aqueous solution); Me (methyl); MeOH (methanol); Et (ethyl); EtOH (ethanol); tBu (t-

butyl); TsCl (p-toluenesulfonyl chloride); Ac (acetyl); AcOH (acetic acid); Ph (phenyl); DIEA (diisopropylethylamine).

Test Method

In order to show the usefulness of the compound [I] of the invention, the pharmacological test result of the representative compound of the present invention is shown in the following.

Test 1: Determination of histone deacetylase inhibitor activity

The partial purification of human histone deacetylase, the preparation of [^{3}H] acetyl histones, and the assay for histone deacetylase activity were performed basically according to the method as proposed by Yoshida et al. as follows.

Partial purification of human histone deacetylase

The human histone deacetylase was partially purified from human T cell leukemia Jurkat cells. Jurkat cells (5 x 10^8 cells) were suspended in 40 mL of the HDA buffer consisting of 15 mM potassium phosphate, pH 7.5, 5% glycerol and 0.2 mM EDTA. After homogenization, nuclei were collected by centrifugation (35, 000 x g, 10 min) and homogenized in 20 mL of the same buffer supplemented with 1 M $(NH_4)_2SO_4$. The viscous homogenate was sonicated and clarified by centrifugation (35,000 x g, 10 min), and the deacetylase was precipitated by raising the concentration of $(NH_4)_2SO_4$ to 3.5 M. The precipitated protein was dissolved in 10 mL of the HDA buffer and dialyzed against 4 liters of the same buffer. The dialyzate was then loaded onto a DEAE-cellulose (Whatman DE52) column (25 x 85 mm) equilibrated with the same buffer and eluted with 300 mL of a linear gradient (0-0.6 M) of NaCl. A single peak of histone deacetylase activity appeared between 0.3 and 0.4 M NaCl.

Preparation of [^{3}H] acetyl histone

To obtain [^{3}H] acetyl-labeled histone as the substrate for the histone deacetylase assay, 1 x 10^8 cells of Jurkat in 20 mL of RPMI-1640 medium (supplemented with 10% FBS, penicillin (50 units/mL) and streptomycin (50 μg/mL)) were incubated with 300 MBq [^{3}H] sodium acetate in the presence of 5 mM sodium butyrate for 30 minutes in 5% CO_2-95% air atmosphere at 37°C in a 75 cm^2 flask, harvested into a centrifuge tube (50 mL), collected by centrifugation at 1000 rpm for 10 minutes, and washed once with phosphate-buffered saline. The washed cells were suspended in 15 mL of ice-cold lysis buffer (10 mM Tris-HCl, 50 mM sodium bisulfite,

1% Triton X-100, 10 mM $MgCl_2$, 8.6% sucrose, pH 6.5). After Dounce homogenization (30 stroke), the nuclei were collected by centrifugation at 1000 rpm for 10 minutes, washed 3 times with 15 mL of the lysis buffer, and once with 15 mL of ice-cooled washing buffer (10 mM Tris-HCl, 13 mM EDTA, pH 7.4) successively. The pellet was suspended in 6 mL of ice-cooled water using a mixer, and 68 µl of H_2SO_4 was added to the suspension to give a concentration of 0.4 N. After incubation at 4°C for 1 hour, the suspension was centrifuged for 5 minutes at 15, 000 rpm, and the supernatant was taken and mixed with 60 mL of acetone. After overnight incubation at -20°C, the coagulated material was collected by microcentrifugation, air-dried, and stored at -80°C.

Assay for histone deacetylase activity

For the standard assay, 10 µl of [^{3}H] acetyl-labeled histones were added to 90 µl of the enzyme fraction, and the mixture was incubated at 25°C for 30 minutes. The reaction was stopped by addition of 10 µl of HCl. The released [^{3}H] acetic acid was extracted with 1 mL of ethyl acetate, and 0.9 mL of the solvent layer was taken into 10 mL of toluene scintillation solution for determination of radioactivity.

Test 2: Determination of T-cell growth inhibitor activity

The T lymphocyte blastogenesis test was performed in microtiter plates with each well containing 1.5 x 10^5 splenic cells of Lewis rats in 0.1 mL RPMI-1640 medium supplemented with 10% fetal bovine serum (FBS), 50 mM 2-mercaptoethanol, penicilln (100 units/mL) and streptomycin (100 µg/mL), to which Concanavalin A (1 µg/mL) was added. The cells were incubated at 37°C in a humidified atmosphere of 5% CO_2 for 72 hours. After the culture period, suppressive activities of the test compounds in T lymphocyte blastogenesis were quantified by AlamarBlue (trademark) Assay. The test samples were dissolved in DMSO and further diluted with RPMI-1640 medium and added to the culture. The activities of the test compounds were expressed as IC_{50}.

The results of those tests are shown in the Table 1.

Table 1: HDAC inhibitory activity and T-cell growth inhibitory activity of the compound of the present invention

Examples	Test 1: HDAC inhibitory activity IC_{50} (nM)	Test 2: T-cell growth inhibitory activity IC_{50} (nM)
Compound E3	140	160
Compound E5	96	310
Compound E6	150	150

The pharmaceutical composition of the present invention comprising histone deacetylase inhibitor such as the compound [I] is useful as a therapeutic or prophylactic agent for diseases caused by abnormal gene expression, such as inflammatory disorders, diabetes, diabetic complications, homozygous thalassemia, fibrosis, cirrhosis, acute promyelocytic leukaemia (APL), protozoal infection and the like. Further, it is useful as an antitumor agent or immunosuppressant, which prevents an organ transplant rejection and autoimmune diseases as exemplified below.

Rejection reactions by transplantation of organs or tissues such as the heart, kidney, liver, bone marrow, skin, cornea, lung, pancreas, small intestine, limb, muscle, nerve, intervertebral disc, trachea, myoblast, cartilage, and the like;
graft-versus-host reactions following bone marrow transplantation;
autoimmune diseases such as rheumatoid arthritis, systemic lupus erythematosus, Hashimoto's thyroiditis, multiple sclerosis, myasthenia gravis, type I diabetes, and the like; and
infections caused by pathogenic microorganisms (e.g. Aspergillus fumigatus, Fusarium oxysporum, Trichophyton asteroides, and the like).

Furthermore, pharmaceutical preparations of the histone deacetylase inhibitor, such as the compound [I], are useful for the therapy or prophylaxis of the following diseases.

Inflammatory or hyperproliferative skin diseases or cutaneous manifestations of immunologically-mediated diseases (e.g.

psoriasis, atopic dermatitis, contact dermatitis, eczematoid dermatitis, seborrheic dermatitis, lichen planus, pemphigus, bullous pemphigoid, epidermolysis bullosa, urticaria, angioedema, vasculitides, erythema, dermal eosinophilia, lupus erythematosus, acne, and alopecia areata);

autoimmune diseases of the eye (e.g. keratoconjunctivitis, vernal conjunctivitis, uveitis associated with Behcet's disease, keratitis, herpetic keratitis, conical keratitis, corneal epithelial dystrophy, keratoleukoma, ocular premphigus, Mooren's ulcer, scleritis, Grave's ophthalmopathy, Vogt-Koyanagi-Harada syndrome, keratoconjunctivitis sicca (dry eye), phlyctenule, iridocyclitis, sarcoidosis, endocrine ophthalmopathy, and the like);

reversible obstructive airways diseases [asthma (e.g. bronchial asthma, allergic asthma, intrinsic asthma, extrinsic asthma, and dust asthma), particularly chronic or inveterate asthma (e.g. late asthma and airway hyper-responsiveness) bronchitis, and the like];

mucosal or vascular inflammations (e.g. gastric ulcer, ischemic or thrombotic vascular injury, ischemic bowel diseases, enteritis, necrotizing enterocolitis, intestinal damages associated with thermal burns, leukotriene B4-mediated diseases);

intestinal inflammations/allergies (e.g. coeliac diseases, proctitis, eosinophilic gastroenteritis, mastocytosis, Crohn's disease and ulcerative colitis);

food-related allergic diseases with symptomatic manifestation remote from the gastrointestinal tract (e.g. migrain, rhinitis and eczema);

renal diseases (e.g. intestitial nephritis, Goodpasture's syndrome, hemolytic uremic syndrome, and diabetic nephropathy);

nervous diseases (e.g. multiple myositis, Guillain-Barre syndrome, Meniere's disease, multiple neuritis, solitary neuritis, cerebral infarction, Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis (ALS), and radiculopathy);

cerebral ischemic diseases (e.g., head injury, hemorrhage in brain (e.g., subarachnoid hemorrhage, intracerebral hemorrhage), cerebral thrombosis, cerebral embolism, cardiac arrest, stroke, transient ischemic attack (TIA), and hypertensive encephalopathy);

endocrine diseases (e.g. hyperthyroidism, and Basedow's disease);

hematic diseases (e.g. pure red cell aplasia, aplastic anemia,

hypoplastic anemia, idiopathic thrombocytopenic purpura, autoimmune hemolytic anemia, agranulocytosis, pernicious anemia, megaloblastic anemia, and anerythroplasia);
bone diseases (e.g. osteoporosis);
respiratory diseases (e.g. sarcoidosis, pulmonary fibrosis, and idiopathic interstitial pneumonia);
skin diseases (e.g. dermatomyositis, leukoderma vulgaris, ichthyosis vulgaris, photosensitivity, and cutaneous T-cell lymphoma);
circulatory diseases (e.g. arteriosclerosis, atherosclerosis, aortitis syndrome, polyarteritis nodosa, and myocardosis);
collagen diseases (e.g. scleroderma, Wegener's granuloma, and Sjögren's syndrome);
adiposis;
eosinophilic fasciitis;
periodontal diseases (e.g. damage to gingiva, periodontium, alveolar bone or substantia ossea dentis);
nephrotic syndrome (e.g. glomerulonephritis);
male pattern alopecia, alopecia senile;
muscular dystrophy;
pyoderma and Sezary syndrome;
chromosome abnormality-associated diseases (e.g. Down's syndrome);
Addison's disease;
active oxygen-mediated diseases [e.g. organ injury (e.g. ischemic circulation disorders of organs (e.g. heart, liver, kidney, digestive tract, and the like) associated with preservation, transplantation, or ischemic diseases (e.g. thrombosis, cardial infarction, and the like);
intestinal diseases (e.g. endotoxin shock, pseudomembranous colitis, and drug- or radiation-induced colitis);
renal diseases (e.g. ischemic acute renal insufficiency, chronic renal failure);
pulmonary diseases (e.g. toxicosis caused by pulmonary oxygen or drugs (e.g. paracort, bleomycin, and the like), lung cancer, and pulmonary emphysema);
ocular diseases (e.g. cataracta, iron-storage disease (siderosis bulbi), retinitis, pigmentosa, senile plaques, vitreous scarring, corneal alkali burn);

dermatitis (e.g. erythema multiforme, linear immunoglobulin A bullous dermatitis, cement dermatitis); and
other diseases (e.g. gingivitis, periodontitis, sepsis, pancreatitis, and diseases caused by environmental pollution (e.g. air pollution), aging, carcinogen, metastasis of carcinoma, and hypobaropathy)];
diseases caused by histamine release or leukotriene C4 release;
restenosis of coronary artery following angioplasty and prevention of postsurgical adhesions;
autoimmune diseases and inflammatory conditions (e.g., primary mucosal edema, autoimmune atrophic gastritis, premature menopause, male sterility, juvenile diabetes mellitus, pemphigus vulgaris, pemphigoid, sympathetic ophthalmitis, lens-induced uveitis, idiopathic leukopenia, active chronic hepatitis, idiopathic cirrhosis, discoid lupus erythematosus, autoimmune orchitis, arthritis (e.g. arthritis deformans), or polychondritis);
Human Immunodeficiency Virus (HIV) infection, AIDS;
allergic conjunctivitis;
hypertrophic cicatrix and keloid due to trauma, burn or surgery.

Therefore, the pharmaceutical composition of the present invention is useful for the therapy and prophylaxis of liver diseases [e.g. immunogenic diseases (e.g. chronic autoimmune liver diseases such as autoimmune hepatic diseases, primary biliary cirrhosis or sclerosing cholangitis), partial liver resection, acute liver necrosis (e.g. necrosis caused by toxins, viral hepatitis, shock or anoxia), hepatitis B, non-A non-B hepatitis, hepatocirrhosis, and hepatic failure (e.g. fulminant hepatitis, late-onset hepatitis and "acute-on-chronic" liver failure (acute liver failure on chronic liver diseases))].

The pharmaceutical composition of the present invention can be used in the form of pharmaceutical preparation, for example, in a solid, semisolid or liquid form, which contains the histone deacetylase inhibitor, such as the compound [I], as an active ingredient in admixture with an organic or inorganic carrier or excipient suitable for external, enteral or parenteral administrations. The active ingredient may be compounded, for example, with the usual non-toxic, pharmaceutically acceptable carriers for tablets, pellets, capsules, suppositories, solutions,

emulsions, suspensions, injections, ointments, liniments, eye drops, lotion, gel, cream, and any other form suitable for use.

The carriers which can be used are water, glucose, lactose, gum acacia, gelatin, mannitol, starch paste, magnesium trisilicate, talc, corn starch, keratin, colloidal silica, potato starch, urea and other carriers suitable for use in manufacturing preparations, in a solid, semisolid, or liquid form, and in addition auxiliary, stabilizing, thickening, solubilizing and coloring agents and perfumes may be used.

For applying the composition to human, it is preferable to apply it by intravenous, intramuscular, topical or oral administration, or by a vascular stent impregnated with the compound [I]. While the dosage of therapeutically effective amount of the histone deacetylase inhibitor, such as the compound [I], varies from and also depends upon the age and condition of each individual patient to be treated, when an individual patient is to be treated, in the case of intravenous administration, a daily dose of 0.01-10 mg of the histone deacetylase inhibitor, such as the compound [I], per kg weight of human being, in the case of intramuscular administration, a daily dose of 0.1-10 mg of the histone deacetylase inhibitor, such as the compound of the formula [I], per kg weight of human being, and in the case of oral administration, a daily dose of 0.5-50 mg of the histone deacetylase inhibitor, such as the compound [I], per kg weight of human being, is generally given for treatment.

During the preparation of the above-mentioned pharmaceutical administration forms, the compound [I] or a salt thereof can also be combined together with other immunosuppressive substances, for example repamycin, mycophenolic acid, cyclosporin A, tacrolimus or brequinar sodium.

Hereinafter the reactions in each Preparations and Examples for preparing the compound [I] of the present invention are explained in more detail. The invention should not be restricted by the following Preparations and Examples in any way.

Preparation 1

To a solution of 4-iodophenylacetic acid (1346 mg) in N,N-dimethylformamide (15 mL) was added tert-butyl 2-aminophenylcarbamate (1.07 g), 1-hydroxybenzotriazole (HOBT) (764

mg), 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide hydrochloride (1.08 g), and the mixture was stirred at ambient temperature for 3 hours. The mixture was poured into water and extracted with ethyl acetate. The organic phase was sequentially washed with saturated aqueous ammonium chloride solution, saturated aqueous sodium hydrogen carbonate solution and brine. The organic phase was dried over magnesium sulfate and evaporated in vacuo. The residue was purified by silica gel chromatography eluting with a mixture of hexane and ethyl acetate (4:1 to 2:1) to give Compound (1) as a pale yellow amorphous (2.03 g).

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.50 (3x3H, s), 3.66 (2H, s), 6.62 (1H, brs), 7.07-7.20 (4H, m), 7.33 (1H, m), 7.47 (1H, m), 7.69 (2x1H, d, J=8.3 Hz), 8.00 (1H, brs);
MASS (ES+): m/e 453.

Preparation 2

To a stirred solution of Compound (1) (25.6 g) in ethanol (300 mL) was added concentrated hydrochloric acid (30 mL), and the mixture was refluxed for 1 hour. The solvent was evaporated *in vacuo* azeotropically with toluene. The residual solid was collected with the mixture of ethanol and ethyl acetate (1:10) to give Compound (2) as an orange solid (20.0 g).

^{1}H-NMR (300 MHz, $CDCl_3$, δ): 4.52 (2H, s), 7.30 (2x1H, d, J=8.3 Hz), 7.49-7.57 (2H, m), 7.73-7.82 (4H, m);
MASS (ES+): m/e 335.

Preparation 3

To a stirred solution of Compound (2) (114 mg) in dioxane (3 mL) and 1N-sodium hydroxide (0.8 mL) was added p-toluenesulfonyl chloride (70 mg) at 0°C. The mixture was allowed to warm to ambient temperature and stirred for 30 minutes. Additional p-toluenesulfonyl chloride (70 mg) was added, then 1N-sodium hydroxide (0.5 mL) was added so that the final pH was 9. The mixture was stirred at ambient temperature for 2 hours. The solvent was evaporated *in vacuo* and the resulting solution was exracted with ethyl acetate. The organic phase was washed with brine, dried over magnesium sulfate and evaporated *in vacuo*. The residue was purified by preparative thin layer chromatography (hexane:ethyl acetate=2:1) to give Compound (3) as a pale yellow amorphous (130 mg).

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 2.35 (3H, s), 4.56 (2H, s), 7.05 (2x1H, d, J=8.5 Hz), 7.32-7.44 (4H, m), 7.63-7.70 (3H, m), 7.78 (2x1H, d, J=8.5 Hz), 7.94 (1H, d, J=6.5 Hz);
MASS (ES+): m/e 489.

Preparation 4

To a stirred solution of Compound (3) (1,137 mg) in N,N-dimethylformamide (15 mL) was added acrylic acid (0.8 mL), palladium(II) acetate (26 mg), tris(2-methylphenyl)phosphine (142 mg) and N,N-diisopropylethylamine (1.25 mL). The mixture was stirred at 120°C for 90 minutes. The resulting mixture was allowed to cool to ambient temperature, poured into water and extracted with ethyl acetate. The organic phase was washed with brine, dried over sodium sulfate and concentrated *in vacuo*. The residue was purified by silica column chromatography eluting with a mixture of chloroform and methanol (20:1) to give Compound (4) as a pale yellow amorphous (455 mg).

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 2.32 (3H, s), 4.63 (2H, s), 6.51 (1H, d, J=16 Hz), 7.26-7.44 (6H, m), 7.54-7.69 (4H, m), 7.79 (2x1H, d, J=8.4 Hz), 7.94 (1H, m);
MASS (ES+): m/e 433.

Preparation 5

To a stirred solution of Compound (4) (70 mg) in N,N-dimethylformamide (3 mL) was added 1-hydroxybenzotriazole (HOBT) (26 mg), 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide hydrochloride (37 mg) and O-(tetrahydro-2H-pyran-2-yl)hydroxylamine (23 mg), and the resulting mixture was stirred at ambient temperature for 14 hours. To the reaction mixture were added additional 1-hydroxybenzotriazole (13 mg), 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide hydrochloride (19 mg) and O-(tetrahydro-2H-pyran-2-yl)hydroxylamine (12 mg), and the mixture was stirred for 6 hours. The reaction mixture were diluted with ethyl acetate and washed succesively with water, saturated ammonium chloride solution, saturated sodium hydrogen carbonate solution and brine. The organic phase was dried over magnesium sulfate and concentrated *in vacuo*. The residue was purified by preparative thin layer chromatography (chloroform:methanol=10:1) to give Compound (5) as a white amorphous (503 mg). The Compound (5) was used in Example 1.

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.44-1.76 (6H, m), 3.52 (1H, m), 3.95 (1H, m), 4.19 (1H, m), 4.90 (1H, m), 6.47 (1H, d, J=15.8 Hz), 7.09-7.19 (2H, m), 7.34-7.58 (7H, m), 11.23 (1H, s), 12.30 (1H, s); MASS (ES+): m/e 378.

Preparation 6

To a stirred solution of (4-bromophenyl)acetic acid (80.0 g, 372 mmol) in N,N-dimethylformamide (640 mL) was added acrylic acid t-butyl ester (95.4 g), palladium(II) acetate (1.67 g), triphenylphosphine (3.91 g) and N,N-diisopropylethylamine (162 mL). The mixture was stirred at 100°C for 7 hours. The resulting mixture was allowed to cool to ambient temperature, poured into 1N-hydrochloric acid and extracted with ethyl acetate twice. The combined organic phase was extracted with saturated sodium hydrogen carbonate solution three times. The combined aqueous phase was acidified with concentrated hydrogen chloride to pH 2 and extracted with ethyl acetate. The organic phase was washed with brine, dried over magnesium sulfate and concentrated in vacuo to give Compound (6) as a pale yellow solid (78.1 g).

^{1}H-NMR (300 MHz, $CDCl_3$, δ): 1.53 (9H, s), 3.67 (2H, s), 6.35 (1H, d, J=16 Hz), 7.29 (2H, d, J=8 Hz), 7.47 (2H, d, J=8 Hz), 7.56 (1H, d, J=16 Hz).

Preparation 7

To a solution of Compound (6) (77.7 g), tert-butyl 2-aminophenylcarbamate (61.7 g) and 1-hydroxybenzotriazole (HOBT) (44.0 g) in N,N-dimethylformamide (777 mL) was added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (62.5 g) at 4°C. The mixture was warmed to ambient temperature and stirred for 2 hours. The reaction mixture was added saturated aqueous sodium hydrogencarbonate (777 mL) and water (3.1 L), and extracted with ethyl acetate (1.5 L). The organic layer was washed with 5% aqueous potassium hydrogensulfate (500 mL), saturated aqueous sodium hydrogencarbonate (500 mL) and brine (500 mL), dried over magnesium sulfate, filtered and evaporated in vacuo to give Compound (7) (135 g).

^{1}H-NMR (300 MHz, $CDCl_3$, δ): 1.49 (9H, s), 1.54 (9H, s), 3.74 (2H, s), 6.36 (1H, d, J=16 Hz), 6.66 (1H, brs), 7.10-7.20 (2H, m), 7.33-7.40 (3H, m), 7.44-7.54 (3H, m), 7.57 (1H, d, J=16 Hz), 7.98 (1H, brs).

Preparation 8

A solution of Compound (7) (47.6 g) in 1N-hydrogen chloride in acetic acid (60 mL) was heated at 120°C for 1 hour. The resulting mixture was allowed to cool to ambient temperature and diluted with ethyl acetate. The resulted precipitate was filtered and the residue was washed with ethyl acetate to give Compound (8) (28.9 g).

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 4.56 (2H, s), 6.56 (1H, d, J=16 Hz), 7.48-7.55 (4H, m), 7.59 (1H, d, J=16 Hz), 7.72-7.80 (4H, m).

Preparation 9

To a solution of Compound (8) (50.0 g), O-tetrahydro-2H-pyran-2-ylhydroxylamine (29.8 g) and 1-hydroxybenzotriazole (34.3 g) in N,N-dimethylformamide (795 mL) was added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (39.5 g) at 9°C. The mixture was warmed to ambient temperature and stirred for 2 hours. The reaction mixture was added saturated aqueous sodium hydrogencarbonate (795 mL) and water (3.2 L). The resulting precipitate was collected by filtation, and washed with saturated aqueous sodium hydrogencarbonate (250×2 mL) and water (250×2 mL) to give Compound (9) (57.2 g).

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.48-1.75 (6H, m), 3.48-3.57 (1H, m), 3.89-4.00 (1H, m), 4.20 (2H, s), 4.90 (1H, brs), 6.47 (1H, d, J=16 Hz), 7.07-7.16 (2H, m), 7.34-7.57 (7H, m), 11.2 (1H, brs), 12.3 (1H, brs).

Preparation 10

To a stirred solution of 2-(4-iodobenzyl)-1H-benzimidazole (451 mg) in dimethylformamide (5 ml) was added portionwise sodium hydride (81 mg, 60% oil dispersion) at 0°C. After 30 minutes, benzyl bromide (0.19 mL) was added dropwise to the mixture, and the mixture was stirred for 30 minutes. The resulting mixture was poured into saturated ammonium chloride solution and extracted with ethyl acetate. The organic phase was washed with brine, dried over sodium sulfate, and concentrated *in vacuo*. The residue was purified by preparative thin layer chromatography (chloroform:methanol=10:1) to give Compound (10) as a pale yellow oil (225 mg). In this preparation, a by-product (1-benzyl-2-[1-(4-iodophenyl)-2-phenylethyl]-1H-benzimidazole) (306 mg) was also obtained and was used in Preparation 23 described below.

^{1}H-NMR (300 MHz, $CDCl_3$, δ): 4.18 (2H, s), 5.19 (2H, s), 6.86-6.97

(4H, m), 7.19-7.32 (6H, m), 7.56 (2x1H, J=8.5 Hz), 7.81 (1H, d, J=7.5 Hz);
MASS (ES+): m/e 425.

Preparation 11

Compound (11) was obtained from Compound (10) according to a manner similar to Preparation 4 as a pale yellow oil (142 mg).
^{1}H-NMR (300 MHz, $CDCl_3$, δ): 1.33 (3H, t, J=7 Hz), 4.26 (2H, s), 4.26 (2H, q, J=7 Hz), 5.21 (2H, s), 6.38 (1H, d, J=16 Hz), 6.88-6.96 (2H, m), 7.18-7.32 (8H, m), 7.41 (2x1H, d, J=8 Hz), 7.62 (1H, d, J=16 Hz), 7.81 (1H, d, J=8 Hz);
MASS (ES+): m/e 397.

Preparation 12

To a stirred solution of Compound (11) (140 mg) in methanol (6 mL) was added 1N sodium hydroxide solution (0.71 mL). The mixture was stirred at ambient temperature for 7 hours. The solvent was evaporated *in vacuo*, and the residue was dissolved in water and washed with diethyl ether. The aqueous phase was acidified to pH 3 with hydrochloric acid, and extracted three times with ethyl acetate. The combined organic phase was washed with brine, dried over sodium sulfate and evaporated *in vacuo* to give Compound (12) as a pale yellow powder (111 mg).
^{1}H-NMR (300 MHz, $CDCl_3$, δ): 4.29 (2H, s), 5.23 (2H, s), 6.36 (1H, d, J=15.7 Hz), 6.88-6.96 (2H, m), 7.16-7.34 (8H, m), 7.41 (2x1H, d, J=8 Hz), 7.62 (1H, d, J=15.7 Hz), 7.81 (1H, d, J=7.5 Hz);
MASS (ES+): m/e 368.

Preparation 13

Compound (13) was obtained from Compound (12) according to a manner similar to Preparation 9 as a white amorphous (111 mg).
^{1}H-NMR (300 MHz, $CDCl_3$, δ): 1.52-1.95 (6H, m), 3.61 (1H, m), 3.94 (1H, m), 4.25 (2H, s), 5.02 (1H, m), 5.20 (2H, s), 6.88-6.96 (2H, m), 7.12-7.41 (11H, m), 7.66 (1H, d, J=15.5 Hz), 7.82 (1H, d, J=8 Hz);
MASS (ES+): m/e 468.

Preparation 14

To a stirred solution of 3-phenylpropanoic acid (7.51 g) in acetic acid (70 mL) were added periodic acid (2.39 g), iodine (5.08 g), concentrated sulfuric acid (1.5 mL) and water (10 mL), and the mixture was stirred at 70°C for 7 hours. The solvent was

evaporated *in vacuo*, and the residue was diluted with water and extracted with ethyl acetate. The organic phase was washed with 10% sodium thiosulfate solution twice, then washed with brine, dried over magnesium sulfate and evaporated *in vacuo*. The precipitate was crystallized from ethyl acetate and hexane to give Compound (14) (5.80 g).

^{1}H-NMR (300 MHz, $CDCl_3$, δ): 2.66 (2H, t, J=7 Hz), 2.90 (2H, t, J=7 Hz), 6.97 (2x1H, d, J=8.5 Hz), 7.61 (2x1H, d, J=8.5 Hz);
MASS (ES-): m/e 275.

Preparation 15

Compound (15) was obtained from Compound (14) according to a manner similar to Preparation 1 (9.50 g).

^{1}H-NMR (300 MHz, $CDCl_3$, δ): 1.51 (3x3H, s), 2.64 (2H, t, J=7.5 Hz), 3.00 (2H, t, J=7.5 Hz), 6.69 (1H, s), 7.00 (2x1H, d, J=8.5 Hz), 7.12-7.20 (2H, m), 7.33 (1H, m), 7.45 (1H, m), 7.62 (2x1H, d, J=8.5 Hz), 7.97 (1H, brs);
MASS (ES+): m/e 467.

Preparation 16

Compound (16) was obtained from Compound (15) according to a manner similar to Preparation 2 (1.55 g).

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 3.20 (2H, t, J=7.5 Hz), 3.41 (2H, t, J=7.5 Hz), 7.10 (2x1H, d, J=8.5 Hz), 7.48-7.56 (2H, m), 7.66 (2x1H, d, J=8.5 Hz), 7.74-7.82 (2H, m);
MASS (ES+): m/e 349.

Preparation 17

Compound (17) was obtained from Compound (16) according to a manner similar to Preparation 3 (7.10 g).

^{1}H-NMR (300 MHz, $CDCl_3$, δ): 2.38 (3H, s), 3.18 (2H, t, J=7 Hz), 3.43 (2H, t, J=7 Hz), 7.05 (2x1H, d, J=8.5 Hz), 7.25 (2x1H, d, J=8.5 Hz), 7.30-7.40 (2H, m), 7.61 (2x1H, d, J=8.5 Hz), 7.67 (1H, m), 7.71 (2x1H, d, J=8.5 Hz), 8.03 (1H, m);
MASS (ES+): m/e 503.

Preparation 18

Compound (18) was obtained from Compound (17) according to a manner similar to Preparation 4 (3.59 g).

^{1}H-NMR (300 MHz, $CDCl_3$, δ): 2.38 (3H, s), 3.27 (2H, t, J=7 Hz), 3.47 (2H, t, J=7 Hz), 6.44 (1H, d, J=16 Hz), 7.25 (2x1H, d, J=8 Hz), 7.31-7.40 (4H, m), 7.50 (2x1H, d, J=8 Hz), 7.66-7.81 (4H, m), 8.04

(1H, m);
MASS (ES+): m/e 447.

Preparation 19

Compound (19) was obtained from Compound (18) according to a manner similar to Preparation 5 (2.20 g). The Compound (19) was used in Example 3.

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.46-1.76 (6H, m), 3.08-3.18 (4H, m), 3.53 (1H, m), 3.95 (1H, m), 4.90 (1H, m), 6.45 (1H, d, J=15.5 Hz), 7.08-7.16 (2H, m), 7.31 (2x1H, d, J=8 Hz), 7.40-7.54 (5H, m), 11.21 (1H, s), 12.28 (1H, br);
MASS (ES+): m/e 392.

Preparation 20

To a stirred solution of 1H-benzimidazole (500 mg) in N,N-dimethylformamide (10 mL) was added sodium hydride (186 mg, 60% of oil suspension) at 0°C. After 90 minutes, 4-iodobenzyl bromide was added to the mixture and the mixture was stirred at ambient temperature for 1 hour. The reaction mixture was quenched with saturated ammonium chloride solution, diluted with water and extracted with ethyl acetate. The organic phase was washed with brine, dried over sodium sulfate and concentrated *in vacuo*. The residue was triturated with hexane to give Compound (20) as a white solid. (1.20 g).

^{1}H-NMR (300 MHz, $CDCl_3$, δ): 5.31 (2H, s), 6.92 (2x1H, d, J=8.5 Hz), 7.21-7.33 (3H, m), 7.67 (2x1H, d, J=8.5 Hz), 7.84 (1H, m), 7.95 (1H, s);
MASS (ES+): m/e 335.

Preparation 21

Compound (21) was obtained from Compound (20) according to a manner similar to Preparation 4 (614 mg).

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 5.53 (2H, s), 6.50 (1H, d, J=16 Hz), 7.15-7.24 (2H, m), 7.32 (2x1H, d, J=8.5 Hz), 7.51 (1H, m), 7.52 (1H, d, J=16 Hz), 7.61-7.70 (3H, m), 8.43 (1H, s);
MASS (ES+): m/e 279.

Preparation 22

Compound (22) was obtained from Compound (21) according to a manner similar to Preparation 5 (536 mg). The obtained Compound (22) was used in Example 4.

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.45-1.76 (6H, m), 3.52 (1H, m), 3.94

(1H, m), 4.89 (1H, m), 5.53 (2H, s), 6.46 (1H, d, J=16 Hz), 7.16-7.25 (2H, m), 7.33 (2x1H, d, J=8.5 Hz), 7.44 (1H, d, J=16 Hz), 7.51 (1H, m), 7.54 (2x1H, d, J=8.5 Hz), 7.67 (1H, m), 8.42 (1H, s), 11.24 (1H, s);

MASS (ES+): m/e 378.

Preparation 23

Compound (23) was obtained from the by-product obtained in Preparation 10 according to a manner similar to Preparation 4 (150 mg).

^{1}H-NMR (300 MHz, $CDCl_3$, δ): 1.32 (3H, t, J=7 Hz), 3.35 (1H, dd, J=13.5, 7.5 Hz), 3.85 (1H, dd, J=13.5, 7.5 Hz), 4.25 (2H, q, J=7 Hz), 4.28 (1H, dd, J=7.5, 7.5 Hz), 5.05 (1H, d, J=16.5 Hz), 5.11 (1H, d, J=16.5 Hz), 6.35 (1H, d, J=16 Hz), 6.75 (2x1H, dd, J=7.5, 1 Hz), 6.93-7.00 (2H, m), 7.09-7.38 (13H, m), 7.59 (1H, d, J=16 Hz), 7.91 (1H, d, J=8 Hz);

MASS (ES+): m/e 487.

Preparation 24

Compound (24) was obtained from Compound (23) according to a manner similar to Preparation 12 (135 mg).

^{1}H-NMR (300 MHz, $CDCl_3$, δ): 3.37 (1H, dd, J=13.5, 7.5 Hz), 3.86 (1H, dd, J=13.5, 7.5 Hz), 4.31 (1H, dd, J=7.5, 7.5 Hz), 5.06 (1H, d, J=15.7 Hz), 5.11 (1H, d, J=15.7 Hz), 6.39 (1H, d, J=15.7 Hz), 6.74 (2x1H, d, J=7 Hz), 6.93-7.02 (2H, m), 7.08-7.33 (11H, m), 7.36 (2x1H, d, J=8 Hz), 7.68 (1H, d, J=15.7 Hz), 7.94 (2x1H, d, J=7.5 Hz);

MASS (ES+): m/e 459.

Preparation 25

Compound (25) was obtained from Compound (24) according to a manner similar to Preparation 9 (140 mg). The obtained Compound (25) was used in Example 5.

^{1}H-NMR (300 MHz, $CDCl_3$, δ): 1.55-1.92 (6H, m), 3.35 (1H, dd, J=13.5, 7.5 Hz), 3.64 (1H, m), 3.84 (1H, dd, J=13.5, 7.5 Hz), 3.95 (1H, m), 4.28 (1H, dd, J=7.5, 7.5 Hz), 5.00 (1H, m), 5.04 (1H, d, J=17 Hz), 5.11 (1H, d, J=17 Hz), 6.75 (2x1H, d, J=7 Hz), 6.92-7.00 (2H, m), 7.08-7.37 (14H, m), 7.64 (1H, d, J=15 Hz), 7.90 (1H, d, J=8 Hz);

MASS (ES+): m/e 558.

Preparation 26

Compound (26) was obtained from (3-bromophenyl)acetic acid

according to a manner similar to Preparation 6 (6.20 g).
^{1}H-NMR (300 MHz, $CDCl_3$, δ): 1.53 (3x3H, s), 3.06 (2H, s), 6.37 (1H, d, J=15.8 Hz), 7.25-7.46 (4H, m), 7.56 (1H, d, J=15.8 Hz);
MASS (ES-): m/e 261.

Preparation 27

Compound (27) was obtained from Compound (26) according to a manner similar to Preparation 7 (6.96 g).
^{1}H-NMR (300 MHz, $CDCl_3$, δ): 1.48 (3x3H, s), 1.53 (3x3H, s), 3.74 (2H, s), 6.39 (1H, d, J=15.8 Hz), 6.70 (1H, brs), 7.09-7.20 (2H, m), 7.32-7.52 (6H, m), 7.56 (1H, d, J=15.8 Hz), 8.04 (1H, brs):
MASS (ES+): m/e 453.

Preparation 28

Compound (28) was obtained from Compound (27) according to a manner similar to Preparation 8 (4.19 g).
^{1}H-NMR (300 MHz, DMSO-d_6, δ): 4.58 (2H, s), 6.58 (1H, d, J=16 Hz), 7.42-7.58 (5H, m), 7.58 (1H, d, J=16 Hz), 7.66 (1H, m), 7.74-7.82 (2H, m), 7.87 (1H, brs);
MASS (ES+): m/e 279.

Preparation 29

Compound (29) was obtained from Compound (28) according to a manner similar to Preparation 9 (3.34 g). The obtained Compound (29) was used in Example 6.
^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.44-1.76 (6H, m), 3.53 (1H, m), 3.95 (1H, m), 4.20 (2H, s), 4.90 (1H, m), 6.50 (1H, d, J=16 Hz), 7.08-7.16 (2H, m), 7.32-7.60 (7H, m), 11.25 (1H, s), 12.31 (1H, brs);
MASS (ES+): m/e 378.

Preparation 30

Compound (30) was obtained from {4-[(1E)-3-tert-butoxy-3-oxo-1-propenyl]phenyl}acetic acid according to a manner similar to Preparation 1 (324 mg).
^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.48 (3x3H, s), 3.176 (1H, s), 3.723 (1H, s), 5.00 (1H, s), 5.01 (1H, s), 6.51 (1H, d, J=15.7 Hz), 6.82 (1H, m), 7.19-7.60 (10H, m), 7.66 (2x1H, d, J=8 Hz), 9.45 (0.5H, s), 9.47 (0.5H, s);
MASS (ES+): m/e 429.

Preparation 31

Compound (31) was obtained from Compound (30) according to a manner similar to Preparation 8 (216 mg).

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 4.59 (2H, s), 6.57 (1H, d, J=16 Hz), 7.42 (1H, m), 7.51 (2x1H, d, J=7.5 Hz), 7.53 (2x1H, d, J=8.5 Hz), 7.60 (1H, d, J=16 Hz), 7.69-7.88 (6H, m), 7.96 (1H, s);
MASS (ES+): m/e 355.

Preparation 32

Compound (32) was obtained from Compound (31) according to a manner similar to Preparation 9 (231 mg). The obtained Compound (32) was used in Example 7.

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.46-1.78 (6H, m), 3.52 (1H, m), 3.95 (1H, m), 4.22 (2H, s), 4.90 (1H, m), 6.48 (1H, d, J=15 Hz), 7.30-7.81 (13H, m), 11.23 (1H, s), 12.38 (1/2H, s), 12.41 (1/2H, s);
MASS (ES+): m/e 454.

Example 1

To a stirred solution of Compound (5) (125 mg) in methanol (5 mL) was added hydrogen chloride methanol reagent 10 (0.5 mL, manufactured by Tokyo Kasei Kogyo Co., Ltd.), and the mixture was stirred at ambient temperature for 30 minutes. The solvent was evaporated in vacuo and the residue was triturated with the mixture of methanol and ethyl acetate (1:2) to give Compound E1 as a white solid (81 mg).

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 4.57 (2H, s), 6.50 (1H, d, J=15.7 Hz), 7.41-7.56 (5H, m), 7.60 (2x1H, d, J=8 Hz), 7.73-7.81 (2H, m), 10.84 (1H, br);
MASS (ES+): m/e 294.

Example 2

Compound E2 was obtained from Compound (13) according to a manner similar to Example 1 (79 mg).

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 4.76 (2H, s), 5.82 (2H, s), 6.49 (1H, d, J=16 Hz), 7.12-7.21 (2H, m), 7.26-7.34 (3H, m), 7.38-7.62 (7H, m), 7.73 (1H, dd, J=7, 1.5 Hz), 7.83 (1H, dd, J=7, 1.5 Hz);
MASS (ES+): m/e 384.

Example 3

Compound E3 was obtained from Compound (19) according to a manner similar to Example 1 (1.74 mg).

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 3.28 (2x1H, t, J=7.5 Hz), 3.47 (2x1H, t, J=7.5 Hz), 6.45 (1H, d, J=16 Hz), 7.32 (2x1H, d, J=8 Hz), 7.41 (1H, d, J=16 Hz), 7.46-7.60 (4H, m), 7.73-7.83 (2H, m), 10.80 (1H, s), 15.10 (1H, br);

MASS (ES+): m/e 308.

Example 4

Compound E4 was obtained from Compound (22) according to a manner similar to Example 1 (377 mg).

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 5.79 (2H, s), 6.50 (1H, d, J=16 Hz), 7.43 (1H, d, J=16 Hz), 7.48-7.64 (6H, m), 7.86-7.94 (2H, m), 9.84 (1H, s);

MASS (ES+): m/e 294.

Example 5

Compound E5 was obtained from Compound (25) according to a manner similar to Example 1 (102 mg).

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 3.31 (1H, m), 3.70 (1H, dd, J=13, 8 Hz), 4.74 (1H, br-t, J=8 Hz), 5.34 (1H, d, J=17 Hz), 5.41 (1H, d, J=17 Hz), 6.37 (1H, d, J=15.5 Hz), 6.73 (2x1H, d, J=6.5 Hz), 7.07-7.45 (16H, m), 7.71 (1H, d, J=7.5 Hz), 9.02 (1H, brs), 10.73 (1H, brs);

MASS (ES+): m/e 474.

Example 6

Compound E6 was obtained from Compound (29) according to a manner similar to Example 1 (1.88 mg).

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 4.57 (2H, s), 6.51 (1H, d, J=16 Hz), 7.40-7.56 (6H, m), 7.68 (1H, s), 7.73-7.81 (2H, m), 10.88 (1H, s);

MASS (ES+): m/e 294.

Example 7

Compound E7 was obtained from Compound (32) according to a manner similar to Example 1 (162 mg).

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 4.58 (2H, s), 6.50 (1H, d, J=15.7 Hz), 7.38-7.56 (6H, m), 7.61 (2x1H, d, J=8 Hz), 7.73 (2x1H, d, J=7 Hz), 7.78-7.88 (2H, m), 7.96 (1H, s), 10.84 (1H, s);

MASS (ES+): m/e 370.

The compounds obtained by the above-mentioned Preparations and Examples are listed in the following Table 2 (including Tables 2-1 to 2-4) and Table 3.

Table 2

Table 2-1

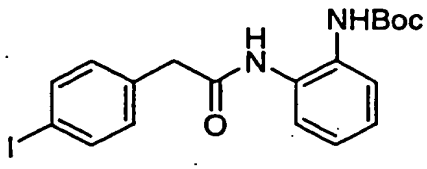
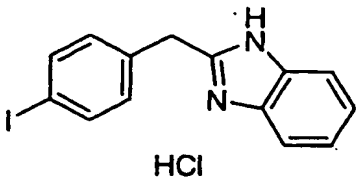
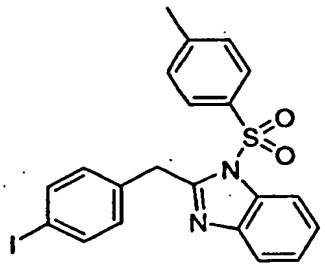
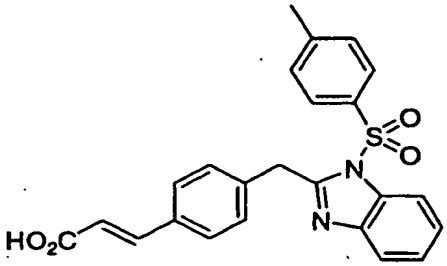
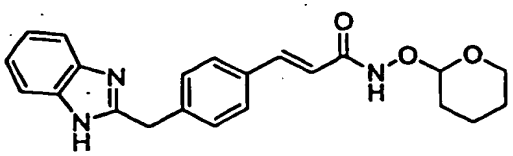
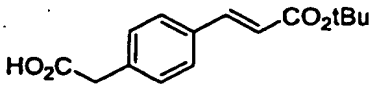
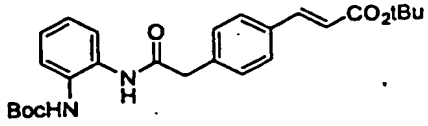
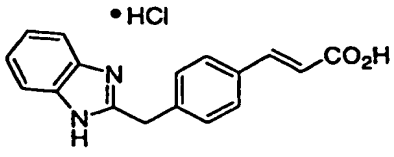
Compound (1)	Compound (2)
	
Compound (3)	**Compound (4)**
	
Compound (5)	**Compound (6)**
	
Compound (7)	**Compound (8)**
	

Table 2-2

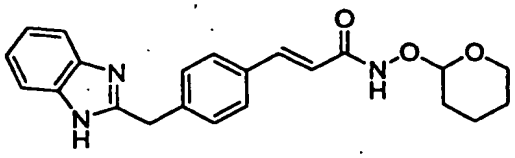
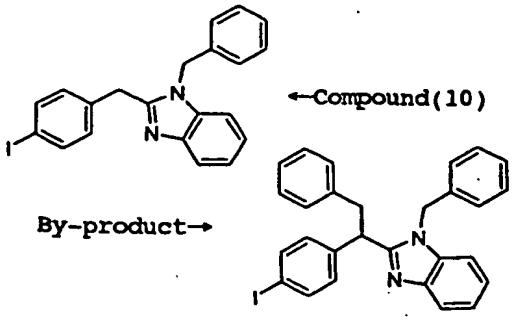
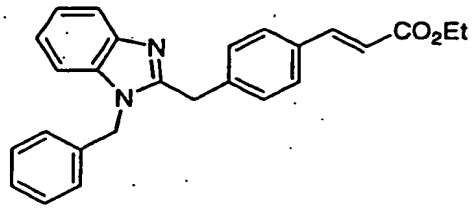
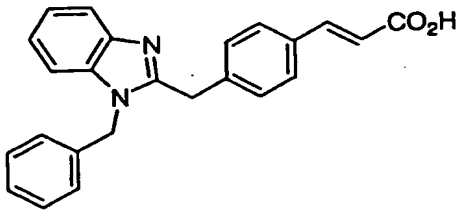
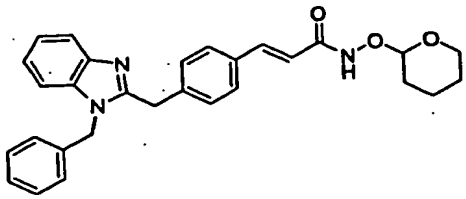
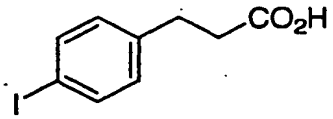
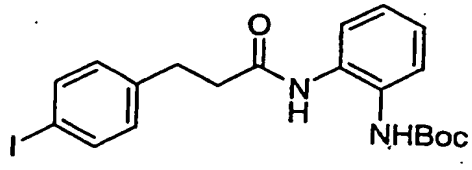
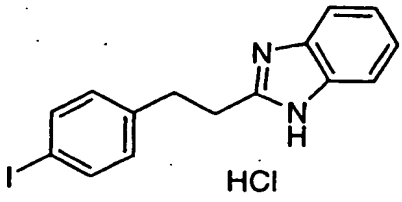
Compound (9)	Compound (10)
	
Compound (11)	**Compound (12)**
	
Compound (13)	**Compound (14)**
	
Compound (15)	**Compound (16)**
	

Table 2-3

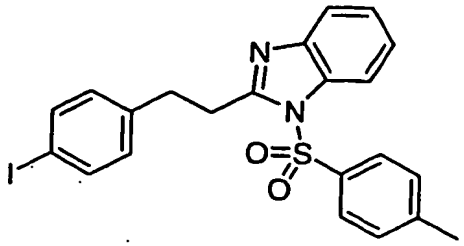
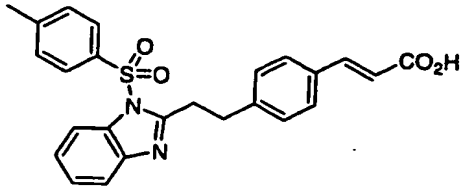
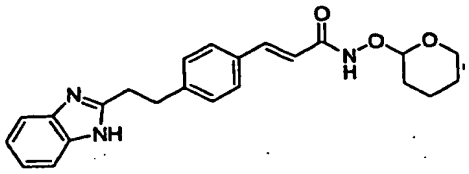
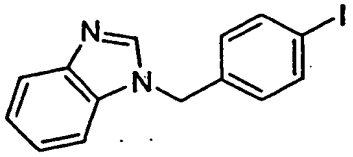
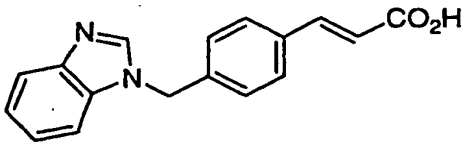
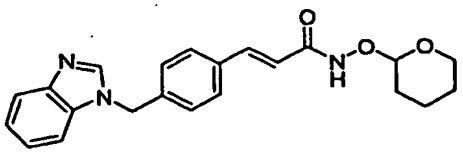
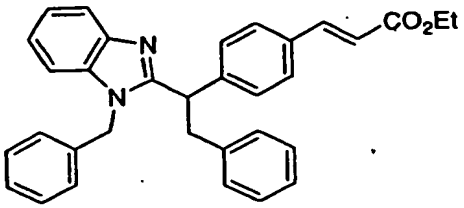
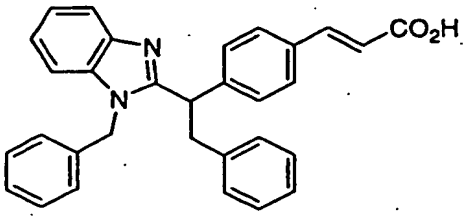
Compound (17)	Compound (18)
	
Compound (19)	**Compound (20)**
	
Compound (21)	**Compound (22)**
	
Compound (23)	**Compound (24)**
	

Table 2-4

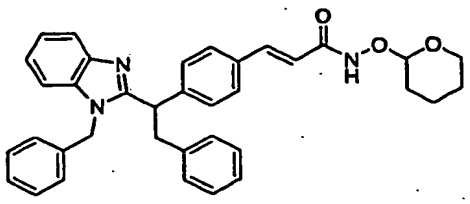
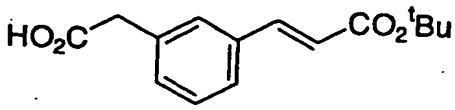
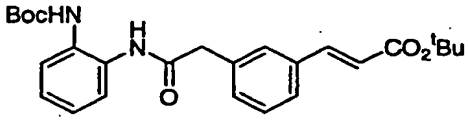
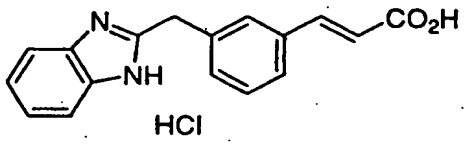
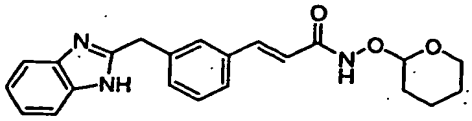
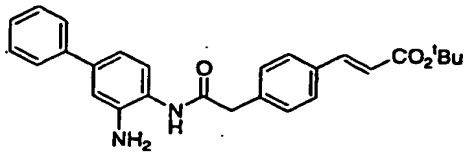
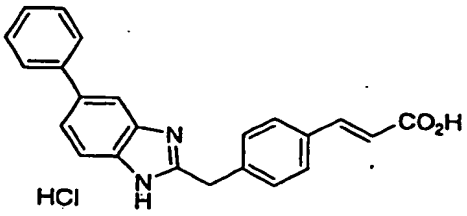
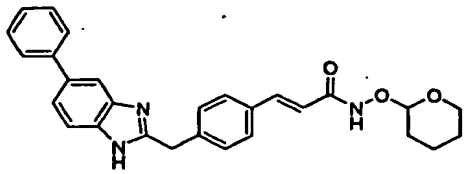
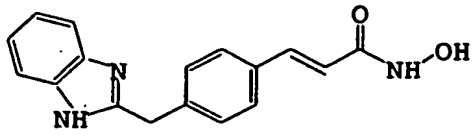
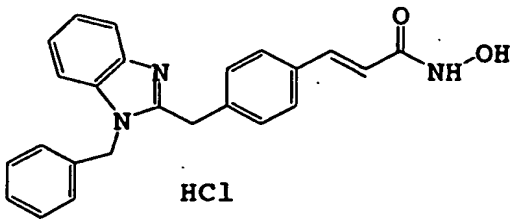
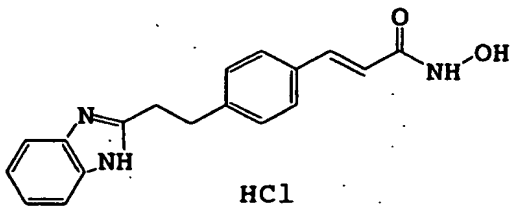
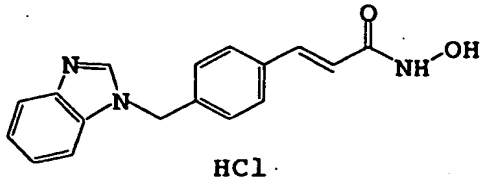
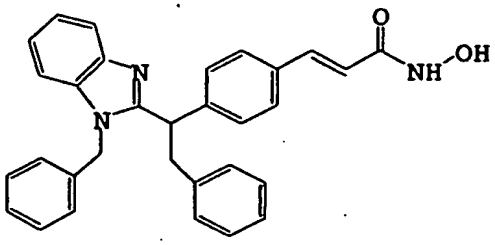
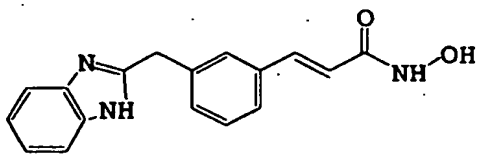
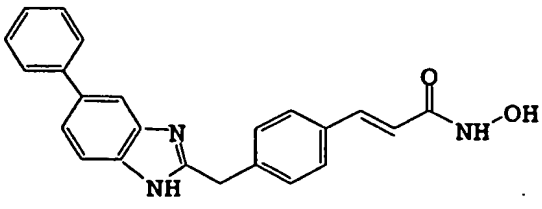
Compound (25)	Compound (26)
	
Compound (27)	**Compound (28)**
	
Compound (29)	**Compound (30)**
	
Compound (31)	**Compound (32)**
	

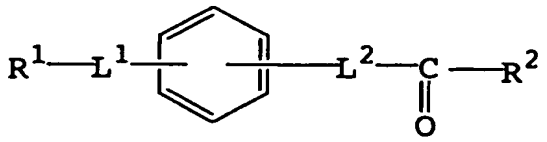
Table 3

Compound E1	Compound E2
 HCl	 HCl
Compound E3	**Compound E4**
 HCl	 HCl
Compound E5	**Compound E6**
	 HCl
Compound E7	
 HCl	

Throughout this specification and the claims which follow, unless the context requires otherwise, the word "comprise", and variations such as "comprises" and "comprising", will be understood to imply the inclusion of a stated integer or step or group of integers or steps but not the exclusion of any other integer or step or group of integers or steps.

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. A compound having the following formula (I):



(I)

wherein

R^1 is N-containing condensed heterocyclic ring optionally substituted with one or more suitable substituent(s),

R^2 is hydroxyamino,

L^1 is $-(CH_2)_n-$ (wherein n is an integer of 0 to 6) optionally substituted with one or more suitable substituent(s), and

L^2 is lower alkenylene,

or a salt thereof.

2. The compound of claim 1, wherein

R^1 is N-containing condensed heterocyclic ring represented by the following formula:

wherein R^3 is hydrogen or a group selected from the group consisting of lower alkyl and aryl, and R^4 is hydrogen or a group selected from the group consisting of lower alkyl and aryl(lower)alkyl,

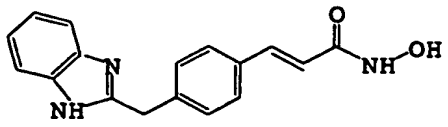
R^2 is hydroxyamino,

L^1 is $-(CH_2)_n-$ (wherein n is 1 or 2) optionally substituted with aryl(lower)alkyl, and

L^2 is vinylene,

or a salt thereof.

3. The compound of claim 2, which is selected from the group consisting of: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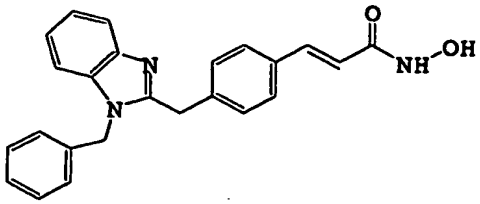
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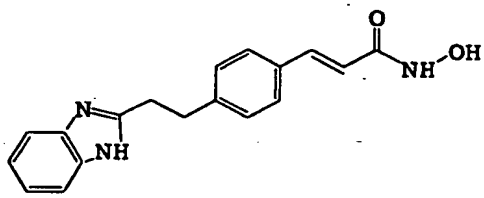
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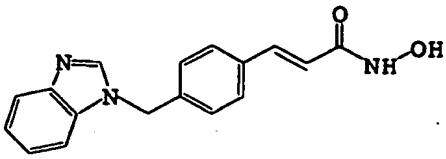
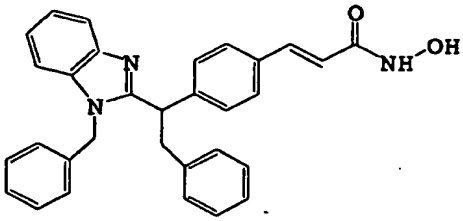

,

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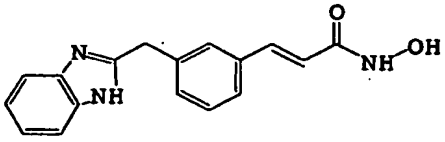
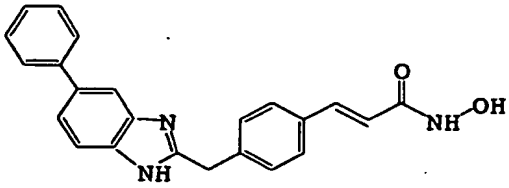
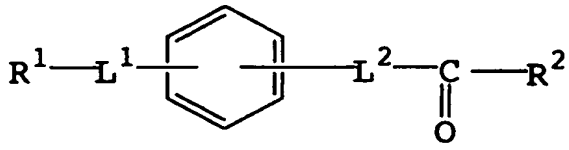

and


or a salt thereof.

4. A pharmaceutical composition containing the compound of any of claims 1 to 3 as an active ingredient, in association with a pharmaceutically acceptable, substantially non-toxic carrier or excipient.

5. The compound of any of claims 1 to 3 for use as a medicament.

6. A histone deacetylase inhibitor comprising a compound having the following formula (I):



(I)

wherein

R^1 is N-containing condensed heterocyclic ring optionally substituted with one or more suitable substituent(s),

R^2 is hydroxyamino,

L^1 is $-(CH_2)_n-$ (wherein n is an integer of 0 to 6) optionally substituted with one or more suitable substituent(s), and

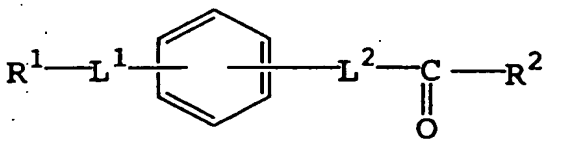
L^2 is lower alkenylene,

or a salt thereof.

7. A method for inhibiting histone deacetylase, comprising using the compound (I) of claim 6.

8. Use of the compound (I) of claim 6 for the manufacture of a medicament for inhibiting histone deacetylase.

9. A pharmaceutical composition for treating or preventing inflammatory disorders, diabetes, diabetic complications, homozygous thalassemia, fibrosis, cirrhosis, acute promyelocytic leukaemia (APL), organ transplant rejections, autoimmune diseases, protozoal infections or tumors, which comprises a compound of the following formula (I) as an active ingredient:



(I)

wherein

R^1 is N-containing condensed heterocyclic ring optionally substituted with one or more suitable substituent(s),

R^2 is hydroxyamino,

L^1 is $-(CH_2)_n-$ (wherein n is an integer of 0 to 6) optionally substituted with one or more suitable substituent(s), and

L^2 is lower alkenylene,

or a salt thereof.

10. A method for treating or preventing inflammatory disorders, diabetes, diabetic complications, homozygous thalassemia, fibrosis, cirrhosis, acute promyelocytic leukaemia (APL), organ transplant rejections, autoimmune diseases, protozoal infections or tumors, which comprises administering an effective amount of the compound (I) of claim 1 to a human being or an animal.

11. Use of the compound (I) of claim 1 for the manufacture of a medicament for treating or preventing inflammatory disorders, diabetes, diabetic complications, homozygous thalassemia, fibrosis, cirrhosis, acute promyelocytic leukaemia (APL), organ transplant rejections, autoimmune diseases, protozoal infections or tumors.

12. A commercial package comprising the pharmaceutical composition of claim 9 and a written matter associated therewith, the written matter stating that the pharmaceutical composition may or should be used for treating or preventing inflammatory disorders, diabetes, diabetic complications, homozygous thalassemia, fibrosis, cirrhosis, acute promyelocytic leukaemia (APL), organ transplant rejections, autoimmune diseases, protozoal infections or tumors.

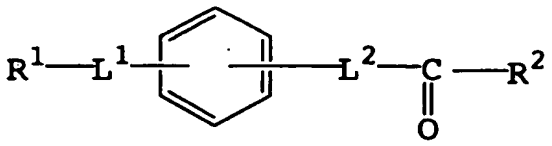
DATED this 13th day of January 2003

Fujisawa Pharmaceutical Co., Ltd.

By DAVIES COLLISON CAVE
Patent Attorneys for the Applicant

ABSTRACT

A compound having the following formula (I):



(I)

wherein

R^1 is N-containing condensed heterocyclic ring optionally substituted with one or more suitable substituent(s),

R^2 is hydroxyamino,

L^1 is $-(CH_2)_n-$ (wherein n is an integer of 0 to 6) optionally substituted with one or more suitable substituent(s), and

L^2 is lower alkenylene, or a salt thereof. The compound is useful as a histone deacetylase inhibitor.